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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,689	09/26/2003	Christine Schmidt	UTAU:1063	9268

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,689	SCHMIDT ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,9-19 and 41-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,9-19 and 41-44* is/are rejected.

7)☒ Claim(s) *1,11,17 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response of 11 July 2007 have been received and entered into the application file. Claims 1, 2, 4, 7, 9, 12-19 and 41-43 have been amended; claims 5, 6, 8 and 20-40 are cancelled; claims 1-4, 7, 9-19 and 41-44 remain pending in the current application, all of which have been considered on the merits.

Priority

Acknowledgement is made of applicant's claim for priority to provisional application 60/414,278, filed 5/27/02.

Response to Arguments

Applicant's response of 11 July 2007 has been fully considered. Objections/rejections not repeated below have been withdrawn from consideration.

With regards to the rejections under 35 USC 112, first and second paragraph, due to unclarity over the charge property of Triton X-200, Applicants have submitted an updated version (2007) of the Sigma Aldrich catalog and a copy of their "Detergent Properties" information sheet, as well as a product information sheet on Triton X-200 from DOW, each of which disclose Triton X-200 to be **anionic**. This information is accepted as accurate, and thus the rejections of record are withdrawn. Any inconvenience is regretted.

With regards to the rejections under 35 USC 102, Applicants have argued that the acellular nerve graft tissue produced by their claimed method is structurally distinct from the acellular grafts of the cited prior art. Applicants point to post-filing date work by Hudson et al (Tissue Engineering, 2004), which provides an in depth discussion of physical properties of acellular grafts prepared by the instant method,

as compared to grafts made by prior art processes, including the graft of Gulati et al. Applicants arguments have been found persuasive, and the rejections of record have been withdrawn; however, new grounds of rejection are made over Sondell et al (Brain Research, 1998).

With regards to the rejections under 35 USC 103, Applicants have amended the claims to limit the tissue to nerve tissue, which is not considered obvious over the teachings of Livesey et al, for the reasons previously discussed. However, new grounds of rejection have been made under 35 USC 103 over Sondell et al (Brain Research, 1998).

Claim Objections

Claim 1 is objected to because the preamble should be limited to a method for preparing a native, acellular nerve replacement, in order to be commensurate in scope with the body of the claim.

Claim 17 is objected to because of a minor informality: to be consistent, the article "a" should be placed before the term "sheet" in the second line, so as to read, "...a tube, a sheet, a scaffold..."

Claim 43 stands objected to, "alloantigenic" is not a recognized term of the art, as it is not found in customary dictionaries, nor defined by (or found in) Applicants' specification, again it is suggested the appropriate intended term is "allogeneic". Correction is required.

Claim 11 is objected to as being dependent on a rejected base claim; however, it would be found allowable if rewritten in independent form to include all limitations of the base claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparing a native, acellular nerve tissue replacement wherein the basal laminae and endoneurium layer retain substantially the native extracellular matrix structure, when Triton X-200 is the anionic detergent used, the specification does not reasonably provide enablement for preparing a nerve tissue replacement, as claimed, when *any* anionic detergent is used. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

It is noted that the specification reports their method of decellularizing nerve tissue grafts by using a combination of sulfobetaines and Triton X-200 results in an acellular tissue graft that better replicates the natural ECM of the native nerve tissue, resulting in an extraordinarily better regenerative capacity, compared to grafts chemically decellularized by the method of Sondell et al (See PGPub, Pg. 12, paragraph 0108). The method of Sondell et al relies on chemical treatment using sodium deoxycholate. The Sondell et al process does not produce grafts which "have a basal laminae and endoneurium layer that retain substantially the native extracellular matrix and structure and integrity," but rather the sodium deoxycholate causes destruction of the ECM structure. Sodium deoxycholate is an anionic detergent. The instant claims 41 and 42 generically recite 'anionic detergent', thus these methods are not limited to use of the anionic detergent Triton X-200. However, based on the evidence provided in the specification, it appears that not any anionic detergent is suitable for preparation of the acellular nerve graft tissues, as claimed, as use of at least sodium deoxycholate will cause disruption of the ECM so that the acellular grafts thereby produced will not satisfy the limitation "wherein the tissue replacement has a basal laminae and endoneurium layer that retain substantially the native extracellular matrix structure and integrity."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7, 9-19 and 41-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In each of independent claims 1, 41 and 42, in lines 7-8 there is technically no antecedent basis for the term "the excess anionic surface-active detergent". It would be remedial to simply delete the word "the".

Claim 9, as currently amended, is rejected because it is unclear how a nerve tissue replacement comprises each of the structures listed in claim 9, particularly a valve, limb replacement or joint. Clarification or correction is required.

Claim 17 is unclear because it requires the native, acellular nerve tissue replacement to further comprise a nerve tissue transplant, it is not clear how these things differ.

Claim 42 is rejected because it is not clear if the method is limited to nerve tissue or is intended to encompass all tissue types. The confusion results because the preamble and body of the claim are generic to any tissue type, yet the newly added final clause refers to the *endoneurium layer* of the tissue replacement, which is specific to nerve tissue. For purposes of examination this limitation is interpreted as limiting the claim to nerve tissue, as that is the only tissue type that would have an endoneurium layer that could meet all the limitations of the claim. However, under this interpretation, claim 42 is considered a substantial duplicate of claim 41. Claims 43 and 44 inherit the deficiencies of claim 42 and are therefore rejected on the same basis.

Duplicate Claim Warning

Applicant is advised that should claim 41 be found allowable, claim 42 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Sondell et al (Brain Research, 1998).

The native, acellular tissue replacement product as claimed is determined to be a product-by-process claim. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Also note that where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, such as instructions pertaining to the use of the product, the content of the printed matter will not distinguish it from the claimed product of the prior art. See *In re Gulack,* 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed Cir. 1983).

Sondell et al disclose an acellular nerve graft produced by substantially the same chemical decellularization process as claimed. The only difference in the methods is that Sondell et al use Triton X-100, a non-ionic detergent, instead of a sulfobetaine, a zwitterionic detergent; however, due to the similar functioning of non-ionic detergents and zwitterionic detergents, such as sulfobetaines (i.e. their ability to solubilize membrane proteins), there is a reasonable expectation that the nerve graft product of Sondell et al is structurally identical to that of instant claim 15.

It is noted that though Sondell et al use sodium deoxycholate, which Applicants have submitted results in a greater disruption of the nerve tissue ECM compared to Triton X-200, however product claims 15-19 are directed to claim 1, which does not specify use of Triton X-200, but rather permits for use of any anionic detergent, including sodium deoxycholate. Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 7, 9, 10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sondell et al (Brain Research, 1998), in view of Hjelmeland (US Patent 4,372,888) and further in view of Atala (US Patent 6,376,244).

Applicant's claim 1 is directed to a method for preparing a native, acellular nerve tissue replacement comprising the steps of: a) obtaining a nerve tissue; b) soaking the nerve tissue for at least six hours in a solution comprising one or more sulfobetaines; c) treating the nerve tissue in a mixture of one or more sulfobetaines with an anionic surface-active detergent; and d) washing the nerve tissue in one or

more solutions of a buffered salt to remove excess anionic surface-active detergent to form the native, acellular nerve tissue replacement with significantly reduced immunologic response.

Sondell et al disclose a chemical decellularization process for preparing acellular nerve tissue replacements involving a series of detergents to disrupt the cell membranes, thereby permitting release and extraction of the cells. Specifically, Sondell et al report obtaining sciatic nerves from dead rats (mammalian cadavers; claim 13); cleaning the excised tissues of fat and blood in several rinses of distilled water (claim 14); soaking the nerve tissue overnight in a solution of Triton X-100 in distilled water; treating the nerve tissue in a solution of sodium deoxycholate (an anionic detergent); followed by a final washing nerves in water; and were then stored in PBS (claim 2) (See Sondell et al, Pg. 45, col. 1: 2.2 Nerve Graft Preparation). The nerve tissue replacements were later implanted into recipient mice to study their ability to promote regeneration (See Sondell et al, Pg. 45, 2.3. Grafting Procedure).

It is noted the storage in PBS can be considered a further washing in a buffered salt solution that reads on the limitation of claim 12 (claim 12). It is further noted the acellular nerve tissue replacement may be considered to comprise a tissue transplant (claim 9)

It is noted Sondell et al use Triton X-100 as the first detergent, not a sulfobetaine. However, sulfobetaine detergents were well known in the art to be suitable for disruption of protein membranes, see, for example, Hjelmeland, (col. 2, ln 10-55). Because both Sondell et al and Hjelmeland teach methods for disrupting cell membranes using detergents, it would have been obvious to one skilled in the art to substitute one method for the other to achieve the predictable result of disrupting the cell membranes. It has been held that substitution of one known element (in the instant case a detergent capable of solubilizing membrane proteins) for another to obtain predictable results (i.e. solubilization of membrane proteins) is prima facie obvious. See *KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (US 2007).*

It is noted that Applicants have previously argued that detergents have individual structures, properties and characteristics, even detergents with the same charge characteristics cannot be used

interchangeably. However, it is respectfully submitted that in the recent KSR International v. Teleflex Co. ruling it was stated that when the examiner provides evidence that different elements (in the instant case, detergents) are recognized in the art as suitable for the same purpose (in the instant case solubilization of membrane proteins), substitution of one element for another is prima facie obvious. Therefore, though Applicants argue that one would not be motivated to 'blindly/randomly' select any one detergent from a list to replace another detergent, nor would one have any reasonable expectation of success, it is submitted that based on the fact that the detergents in question were each recognized in the art as capable of successfully solubilizing membrane proteins, substitution of one detergent for the other (sulfobetaines for Triton X-100) would have been prima facie obvious.

With regards to addition of drugs or bioactive agents, Sondell et al do not report further treating the nerve tissue replacements prior to implantation into recipient mice; however, Atala teaches it is beneficial to add drugs such as glycoproteins, chondroitin-4-sulfate, chondroitin-6-sulfate, dermatan sulfate, keratin sulfate, etc, before seeding cells to decellularized tissue replacement scaffolds before seeding of cells in order to promote cellular adhesion and growth (See Atala, col. 8, ln 55-62). Therefore it would have been obvious to one of ordinary skill in the art to add bioactive agents and drugs, such as chondroitin-4-sulfate, to the decellularized nerve tissue replacement of Sondell et al prior to implantation in order to promote cell adhesion and cell growth so as to improve regeneration (Claims 4 and 7). One of ordinary skill in the art would have been motivated to add drugs to promote cell growth and adhesion in order to ensure cells infiltrate and adhere to the tissue replacement in order to create a functional tissue replacement. One would have expected success adding drugs and bioactive agents to the tissue replacement of Livesey et al because Atala et al teach successfully adding the drugs to a similar acellular tissue replacement (See Atala, col. 8, ln 55-62). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford, Jr/
Primary Examiner
Art Unit 1651